REMARKS

With entry of the present amendment claims 1 to 11, 13, and 15 to 22 are pending. Claims 4, 6, and 19 have been amended to correct obvious typographical errors. Claim 18 has been amended to clarify the final process step. These amendments do not change the scope of the claims. The amended claims are supported by the specification and claims as filed. No new matter has been added.

No additional fees are believed due. However, the Director is hereby authorized to charge any deficit, or credit any overpayment, to Deposit Account No. 08-2525.

OBJECTION OF CLAIM 4, 6, AND 19

Claim 6 has been objected to because the word "peptide" is misspelled. This claim has been amended to correct the misspelling.

Claims 4 and 19 have been objected to because the word "aggregated" is misspelled. These claims have been amended to correct the misspelling.

REJECTION OF CLAIM 18 UNDER 35 U.S.C. 112, SECOND PARAGRAPH

Claim 18 stands rejected under 35 U.S.C. § 112, second paragraph, as indefinite because it is supposedly not clear whether the phrase "with the help of the base-line separated peak patterns..." is a separate step. Claim 18 has been amended to clarify that the base-line separated peak patterns of the natural and stable 15N isotopes are used to determine the amount of β-amyloid present in the source of aggregated β-amyloid. As amended, it is now clear that no separate step is involved with regard to the base-line separated peak patterns.

For at least these reasons, Applicants respectfully request reconsideration and withdrawal of this rejection.

REJECTION OF CLAIMS 1, 2, 9, 11, 15, 16, AND 17 UNDER 35 U.S.C. § 103 OVER CLARKE ET AL. (2001) IN VIEW OF REIK ET AL. (2001)

Claims 1, 2, 9, 11, 15, 16, and 17 stand rejected under 35 U.S.C. § 103 over Clarke et al. (2001) in view of Reik et al. (2001). In making this rejection, the Office Action states that Clarke describes a method for quantifying β-amyloid in guinea pig brain cells by adding a defined amount of synthetically produced β-amyloid peptide to a cell lysate containing naturally produced oxidized β-amyloid, preparing the isolated β-amyloid for analysis by mass spectroscopy, analyzing the prepared β-amyloid by mass spectroscopy, and determining the amount of β-amyloid present in the guinea pig brain cell lysate. The Office Action admits that Clarke does not teach the preparation for analysis by mass spectroscopy by enzymatic digrestion by a protease or use of MALDI-TOF mass spectroscopy. However, the Office Action combines Reik et al to overcome these deficiencies. Reik is said to describe the use of recombinantly produced and labled β-amyloid, wherein the β-amyloid is labeled with N^{15}, and the use of enzymatic digestion with the protease Lys-C prior to analysis by mass spectroscopy. It is said that the claimed invention would have been obvious over the combination of these references on the basis that Clarke could be adapted for the detection and quantification of isotopically labeled β-amyloid.

Applicants respectfully traverse this rejection for the following reasons.

Claim 1 includes the steps of

(a) providing a source of beta amyloid

(b) adding a defined amount of beta amyloid peptide labeled with a stable isotope to the source of (a).

(c) isolating unlabeled and labeled beta amyloid

(d) preparing the isolated beta amyloid for analysis by mass spectrometry

(e) analyzing the prepared beta amyloid peptide by mass spectrometry, and

(f) determining the amount of beta amyloid that was present in the source of beta amyloid.

Thus, the claim requires isolation of labeled and unlabeled β-amyloid. Clarke does not employ a β-amyloid peptide labeled with a stable isotope and, therefore, does not isolate labeled and unlabeled β-amyloid. This is because Clarke is directed to the separation and detection of two different forms of β-amyloid, Aβ1-40 and Aβ1-42. Separation is accomplished by isolating β-amyloid (all unlabeled) from lysed cells. The lysate is passed through SEC separation media which separates substances *on the basis of molecular weight*, thus resulting in separation of the unlabeled Aβ1-40 from the unlabeled Aβ1-42. The ratio of these two forms is then determined.

While Reik et al. does employ an ^{15}N-isotope of two forms of β-amyloid: Aβ1-40 and Aβ1-42, the wild-type and radio-labeled compounds are not mixed together and not isolated as required by the claimed invention. Rather each of the 4 resulting peptides; $A\beta1\text{-}40^{OX}$, $A\beta1\text{-}42^{OX}$, ^{15}N-labeled $A\beta1\text{-}40^{OX}$, and ^{15}N-labeled $A\beta1\text{-}42^{OX}$; are produced and analyzed *separately* by NMR *to determine their structure* in relation to aggregation and ultimate plaque formation of each form. The amount of β-amyloid is never quantified.

Thus, one skilled in the art would not have been motivated to use the radio-labeled β-amyloid of Reik to quantify the amount of β-amyloid in Clarke because (1) radio-labeling would not be necessary for separation by molecular weight as described in Clarke and (2) Reik used radio-labeling for structural determinations, not for quantification. Even if combined, these references would not obviate the claimed invention as the combination does not teach or suggest quantification through the use of a stable isotope. Rather, the combination would suggest determination of the relative amounts of Aβ1-40 and Aβ1-42 via separation by molecular weight and determination of the structure of each of these forms separately using a radiolabeled isotope.

For at least these reasons, Applicants respectfully request reconsideration and withdrawal of this rejection.

REJECTION OF CLAIMS 1, 2, 4, 7, 8, 9, 11, 13, 18, 19, 21, AND 22 UNDER 35 U.S.C. § 103 OVER CLARKE ET AL. (2001) IN VIEW OF REIK ET AL. (2001) AND KAMETANI ET AL. (1999)

Claims 1, 2, 4, 7, 8, 9, 11, 13, 18, 19, 21, and 22 stand rejected under 35 U.S.C. § 103 over Clarke et al. (201) in view of Reik et al. (2001) and Kametani et al. (1999). In making this rejection, the Office Action admits that the combination of Clarke and Reik does not teach the use of β-amyloid from a tissue sample obtained through laser dissection excision, wherein the β-amyloid peptides are either amino or carboxy terminal microheterogenous and combined Kametani et al. to fill this deficiency.

Applicants respectfully traverse this rejection for the following reasons. As noted above, the combination of Clarke and Reik is missing more than the use of β-amyloid from a tissue sample obtained using laser dissection excision in that the combination does not teach quantification of an aggregate of different forms of β-amyloid using a stable isotope. Kametani does not cure these deficiencies. Kametani describes *immunoprecipitation* to determine the relative amounts of one particular length polypeptide of β-amyloid as compared to one other specific length polypeptide of β-amyloid. Kametani et al. accomplishes this determination in a one step process by which a β-amyloid-antibody complex is formed and immunoprecipitated. Measurement of the precipitated β-amyloid-antibody complexes provides a ratio of two different forms of β-amyloid, β1-42 and β1-40. It does not employ a stable isotope, and it does not quantify all of the β-amyloid in the sample, but rather provides a ratio of two specific forms.

Therefore, for the reasons provided above, Applicants submit that the combination of Clarke, Reik, and Kametani does not render the claims obvious, in part, because the combination does not teach quantification of β-amyloid in a sample using a stable isotope.

For at least these reasons, Applicants respectfully request reconsideration and withdrawal of this rejection.

REJECTION OF CLAIM 3 UNDER 35 U.S.C. § 103 OVER CLARKE ET AL. (2001) IN VIEW OF REIK ET AL. (2001) AND KAMETANI ET AL. (1999) FURTHER IN VIEW OF SCHUTZE ET AL. (1998)

Claim 3 stands rejected under 35 U.S.C. § 103 over Clarke et al. (201) in view of Reik et al. (2001) and Kametani et al. (1999) further in view of Schutze et al. (1998). In making this rejection, the Office Action states that Schutze describes laser dissection microscopy to capture samples of any shape and size, including cell clusters and single cells.

Applicants traverse this rejection for the following reasons. Nothing in Schutze overcomes the deficiencies of the combination of Clarke, Reik, and Kametani discussed in response to the rejection above. Therefore, for the reasons provided above, Applicants submit that the combination of Clarke, Reik, Kametani, and Schutze does not render the claims obvious in that the combination of these references does not teach the use of a stable isotope or isolation of labeled and unlabeled β-amyloid.

For at least these reasons, Applicants respectfully request reconsideration and withdrawal of this rejection.

REJECTION OF CLAIMS 5, 6, AND 10 UNDER 35 U.S.C. § 103 OVER CLARKE ET AL. (2001) IN VIEW OF KAMETANI ET AL. (1999) FURTHER IN VIEW OF WANG ET AL (1996)

Claims 5, 6, and 10 stand rejected under 35 U.S.C. § 103 over Clarke et al. (201) in view of Kametani et al. (1999) further in view of Wang et al. (1996). In making this rejection, the Office Action states that the ordinary artisan would have a reasonable expectation of success in combining the techniques of Clarke, Kametani, and Wang.

Applicants respectfully traverse this rejection for the following reasons.

Clarke describes the separation and detection of two different forms of β-amyloid, Aβ1-40 and Aβ1-42. This separation is accomplished by isolating β-amyloid (all unlabeled) from lysed cells. The lysate is passed through SEC separation media which separates substances *on the basis of molecular weight*, thus resulting in separation of the Aβ1-40 from the Aβ1-42. The ratio of these two forms is then determined.

Kametani describes *immunoprecipitation* to determine the relative amounts of one particular length polypeptide of β-amyloid as compared to one other specific length polypeptide of β-amyloid. Kametani et al. accomplishes this determination in a one step process by which a β-amyloid-antibody complex is formed and immunoprecipitated. Measurement of the precipitated β-amyloid-antibody complexes provides a ratio of two different forms of β-amyloid, β1-42 and β1-40.

Neither of these references employs a stable isotope and neither quantifies the total amount of β-amyloid in a sample. Rather, each of these references is concerned with the determination of the ratio of two different forms of β-amyloid: β1-42 and β1-40 through different analytical methods, neither of which employ a stable isotope.

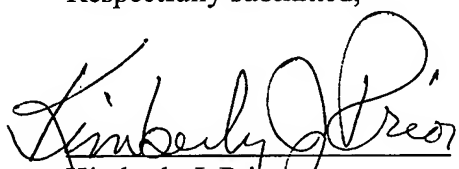
Wang, et al. describes isolation of different forms of β-amyloid by immunoisolation with *β-amyloid specific monoclonal antibodies*. Nothing in Wang cures the deficiencies of the combination of Clarke and Kametani. None of these references describes the use of stable isotopes to quantify β-amyloid nor describes separation of labeled and unlabeled isotopes as required by the claims. Therefore, this combination of references cannot render the claimed invention obvious.

For at least these reasons, Applicants respectfully request reconsideration and withdrawal of this rejection.

The foregoing amendment is fully responsive to the Office Action issued April 24, 2006. Applicants submit that Claims 1 to 11, 13, 15 to 22 are allowable. Early and favorable consideration is earnestly solicited.

If the Examiner believes there are other issues that can be resolved by telephone interview, or that there are any informalities remaining in the application which may be corrected by Examiner's Amendment, a telephone call to the undersigned attorney is respectfully solicited.

Respectfully submitted,



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